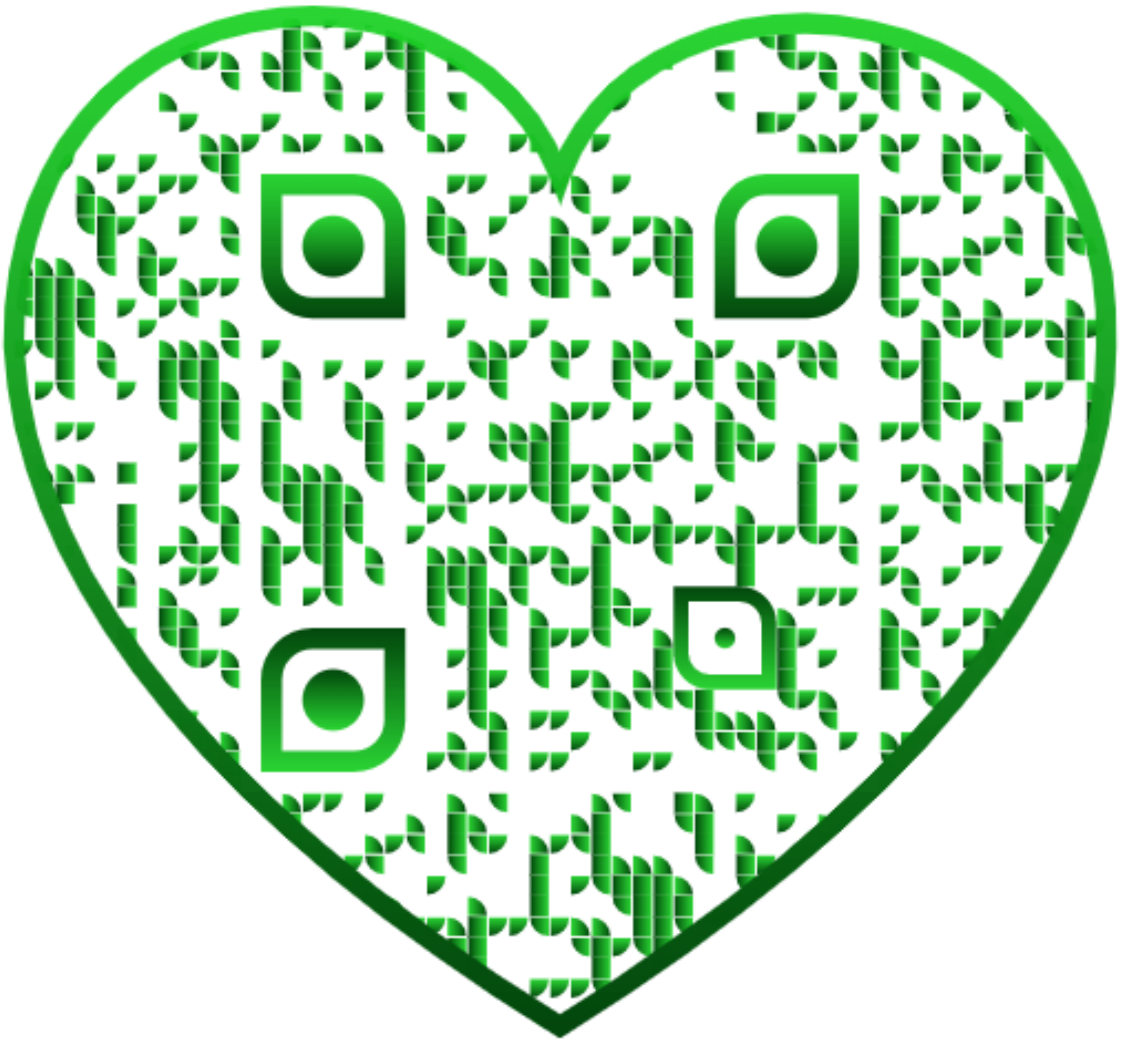
Nucleic acids

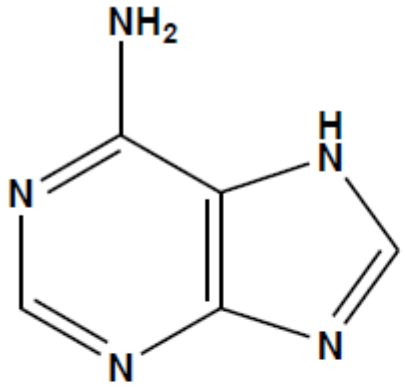
A. Introduction

- Life begins with nucleic acids
- A nucleic acid is naturally occurring chemical compound that is capable of being broken down to yield
  - Phosphoric acid (phosphate group),
  - Sugars (pentose), and
  - a mixture of organic bases (purines and pyrimidines) or nitrogenous bases.

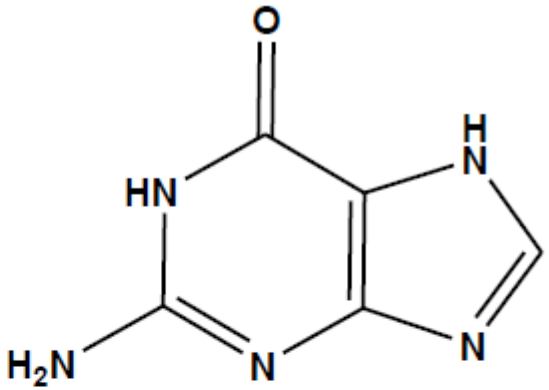


Nucleic acids (int. cont.)

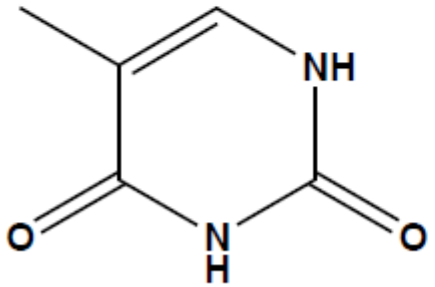
- Five d/t nitrogenous bases in nature
  - **Adenine**, **thymine** (DNA only), **uracil** (RNA only), **cytosine**, and **guanine**.



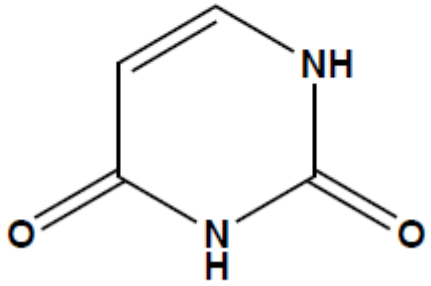
Adenine



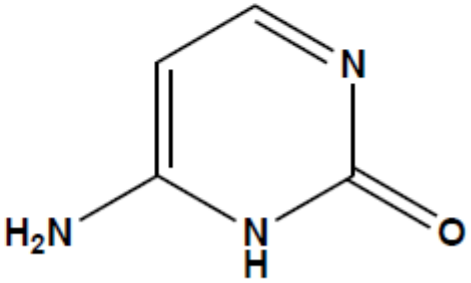
Guanine



Thymine



Uracil



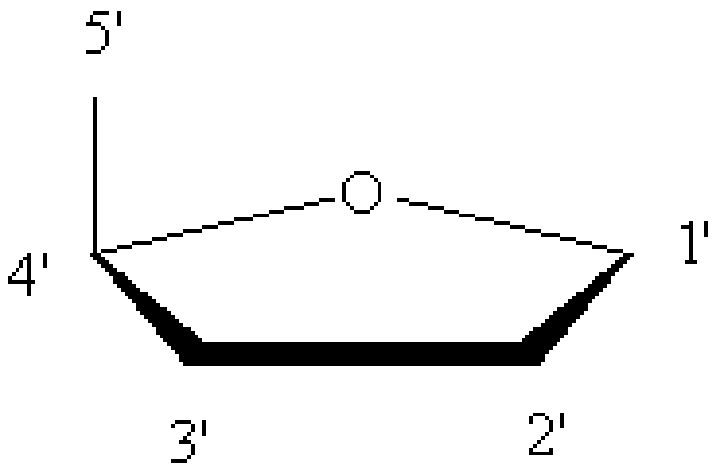
Cytosine

Nitrogenous Bases

- Planar, aromatic, and heterocyclic
- Derived from purine or pyrimidine
- Complex Biosynthetic origin

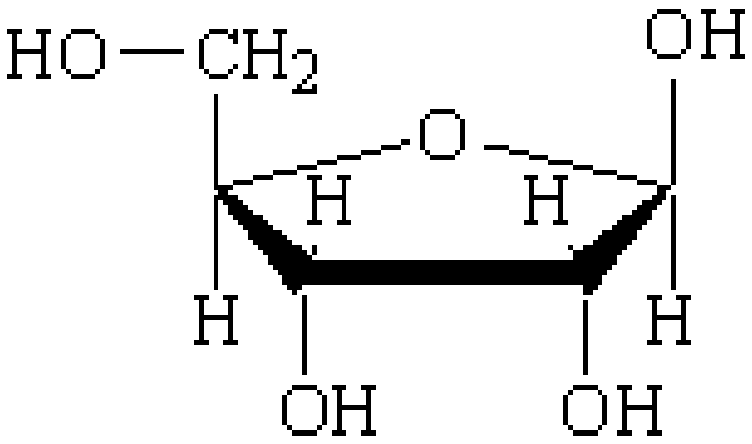
Sugars

- Pentoses (5-C sugars)
- D-Ribose (for RNA) and 2'-Deoxyribose(for DNA)

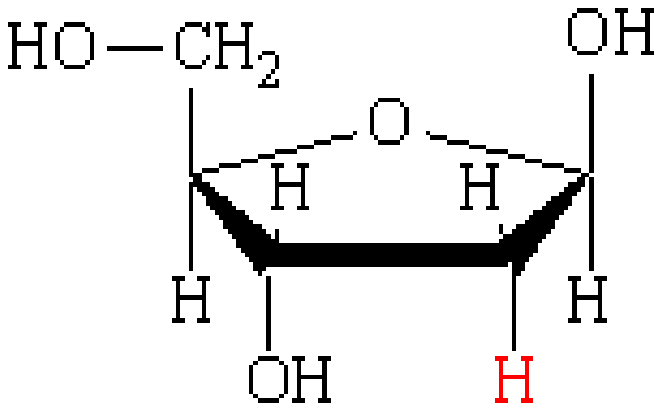


Sugars

D-Ribose and 2'-Deoxyribose



D-Ribose

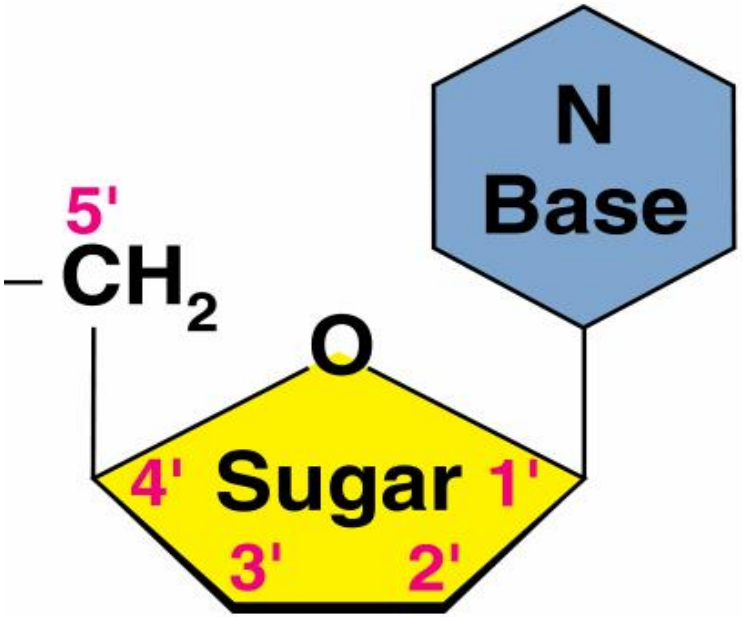


2'-Deoxyribose

Lacks a 2'-OH group

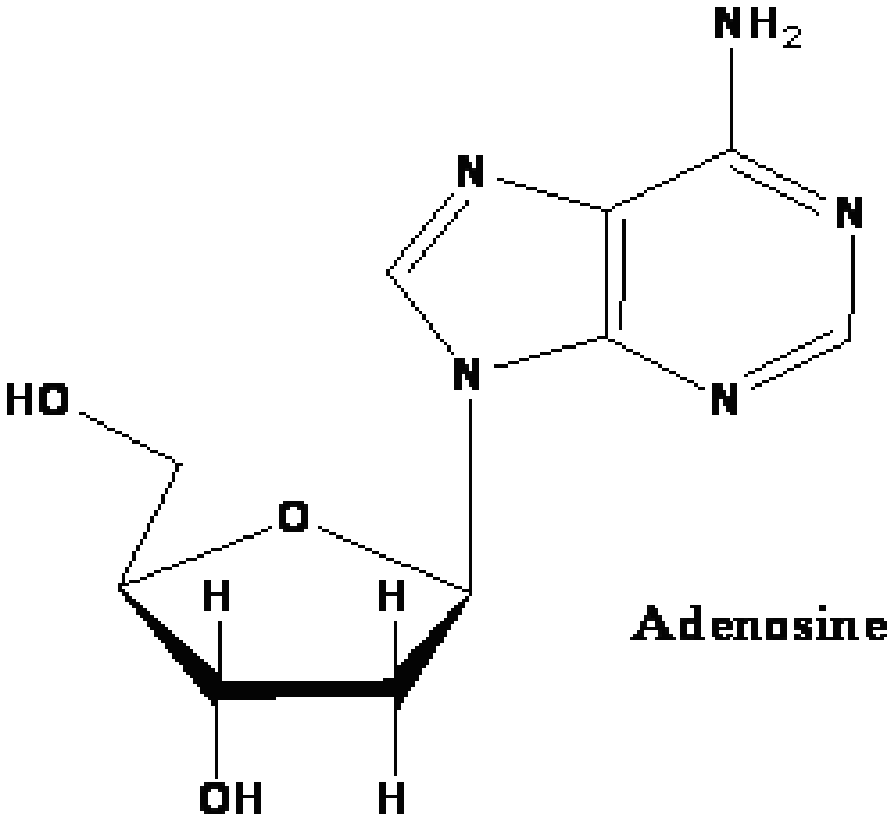
Nucleosides

- Result from linking of one of the sugars with a purine or pyrimidine base through an N-glycosidic linkage



Nucleosides

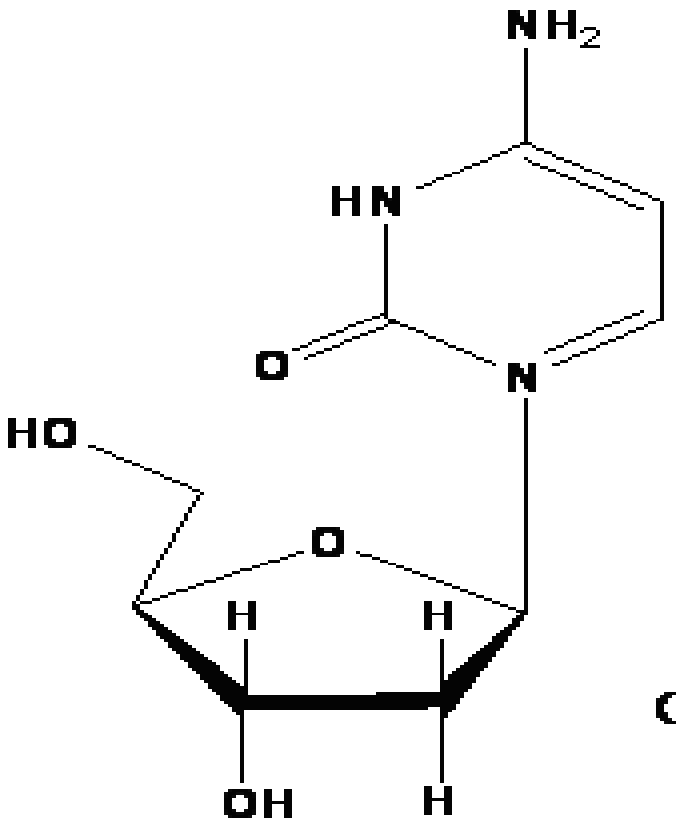
- Purines bond to the C1' carbon of the sugar at their N9 atom



Adenosine

Nucleosides

- Pyrimidines bond to the C1' carbon of the sugar at their N1 atoms



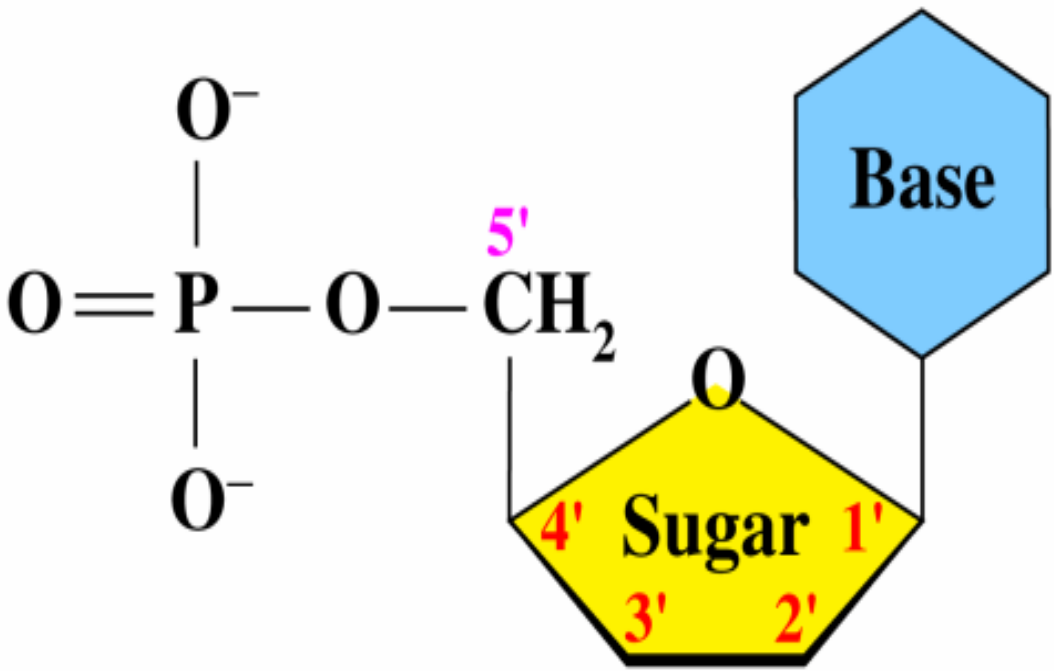
Cytidine

Phosphate Groups

- Phosphates can be bonded to
  - either C-3 or C-5 atoms of the sugar
- Mono-, di- or triphosphates

Nucleotides

- Result from linking one or more phosphates with a nucleoside onto the 5' end of the molecule through esterification



Naming Conventions

- Nucleosides:
  - Purine nucleosides end in “-osine”
    - Adenosine, Guanosine
  - Pyrimidine nucleosides end in “-idine”
    - Thymidine, Cytidine, Uridine

Naming Conventions cont.

- Nucleotides:
  - Start with the nucleoside name and add
    - "mono-", "di-", or "triphosphate"
  - Example,
    - Adenosine Monophosphate,
    - Cytidine Triphosphate,
    - Deoxythymidine Diphosphate

Naming Conventions cont.

Base	Nucleosides	Nucleotides
RNA		
Adenine (A)	Adenosine (A)	Adenosine 5'-monophosphate (AMP)
Guanine (G)	Guanosine (G)	Guanosine 5'-monophosphate (GMP)
Cytosine (C)	Cytidine (C)	Cytidine 5'-monophosphate (CMP)
Uracil (U)	Uridine (U)	Uridine 5'-monophosphate (UMP)
DNA		
Adenine (A)	Deoxyadenosine (A)	Deoxyadenosine 5'-monophosphate (dAMP)
Guanine (G)	Deoxyguanosine (G)	Deoxyguanosine 5'-monophosphate (dGMP)
Cytosine (C)	Deoxycytidine (C)	Deoxycytidine 5'-monophosphate (dCMP)
Thymine (T)	Deoxythymidine (T)	Deoxythymidine 5'-monophosphate (dTMP)

Nucleic acids (cont.)

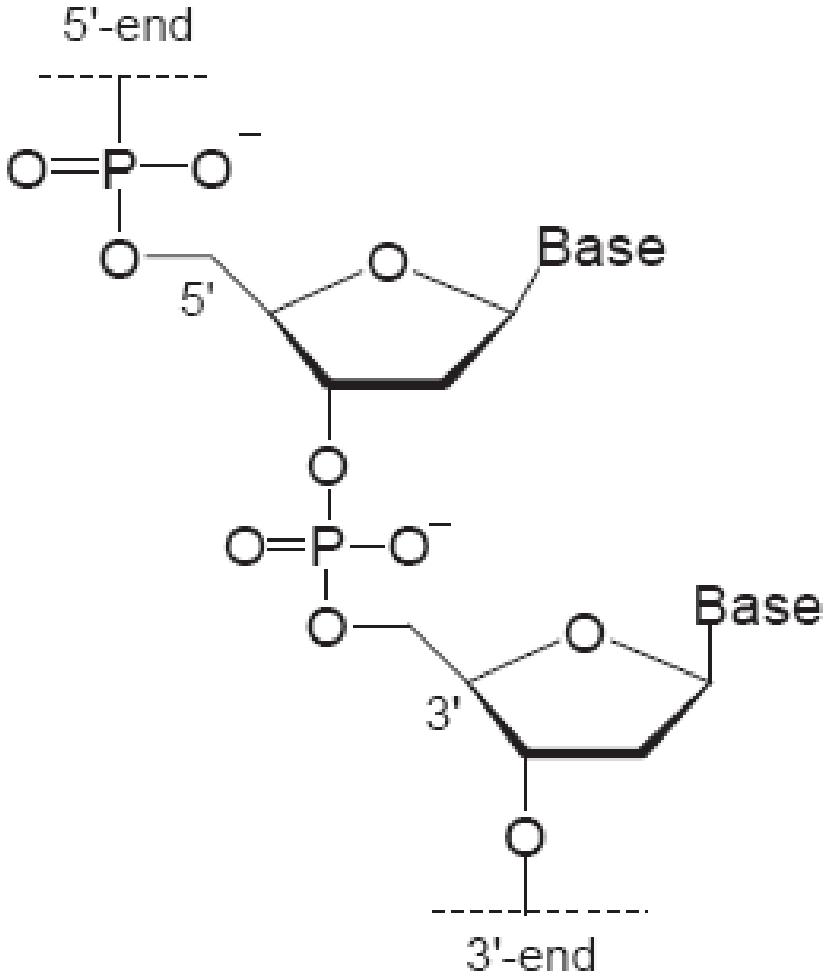
B. Structure of nucleic acids

Primary Structure of Nucleic Acids

- In the **primary structure** of nucleic acids
  - Nucleotides are joined by **phosphodiester bonds**.

Nucleic acids (structure cont.)

The 3'-OH group of the sugar in one nucleotide forms an ester bond to the phosphate group on the 5'-carbon of the sugar of the next nucleotide.



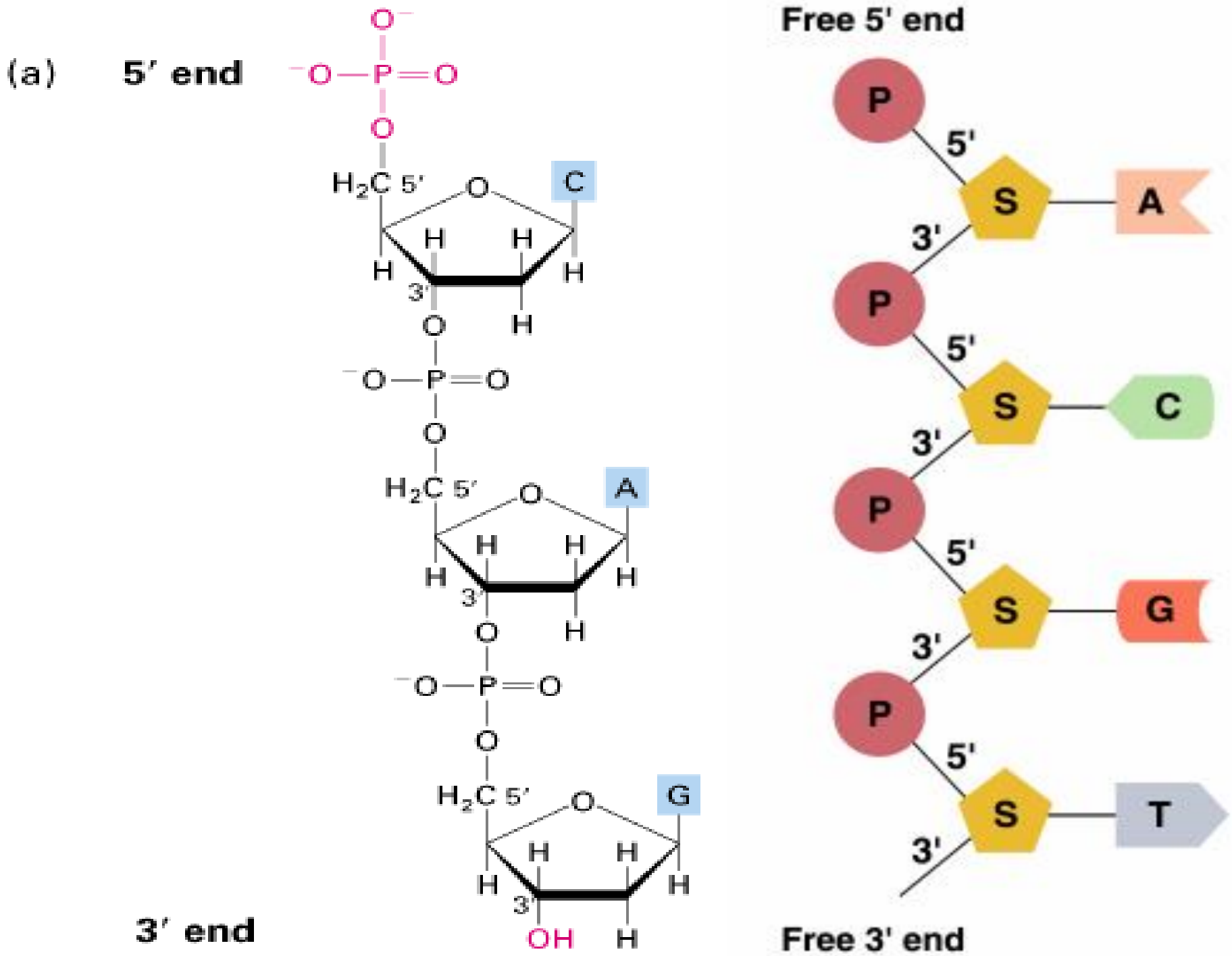
Generalized structure of DNA

Nucleic acids (structure cont.)

- **Nucleic acids' primary strand is directional**
  - Has a free 5'-phosphate group at one end and a free 3'-OH group at the other end.
  - Is read from the free 5'-end using the letters of the bases.

Nucleic acids (structure cont.)

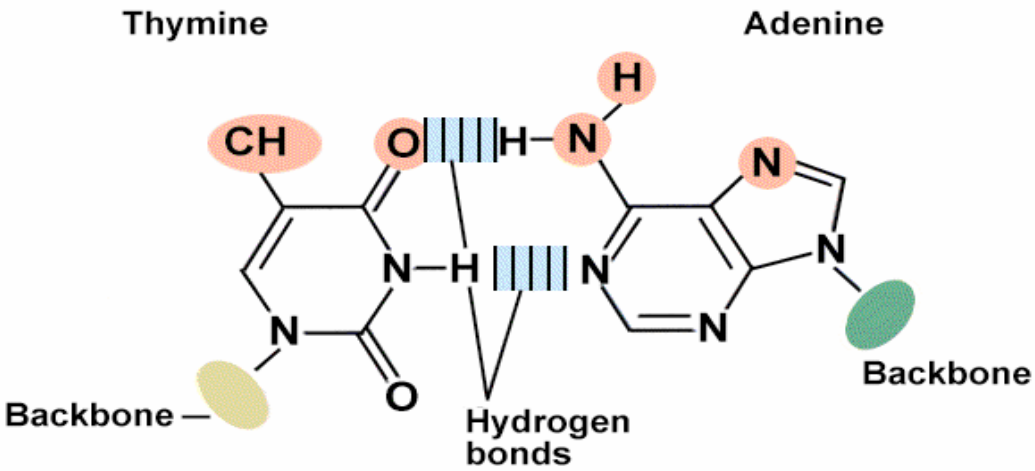
- The following examples read
  - —C—A—G— and
  - —A—C—G—T—

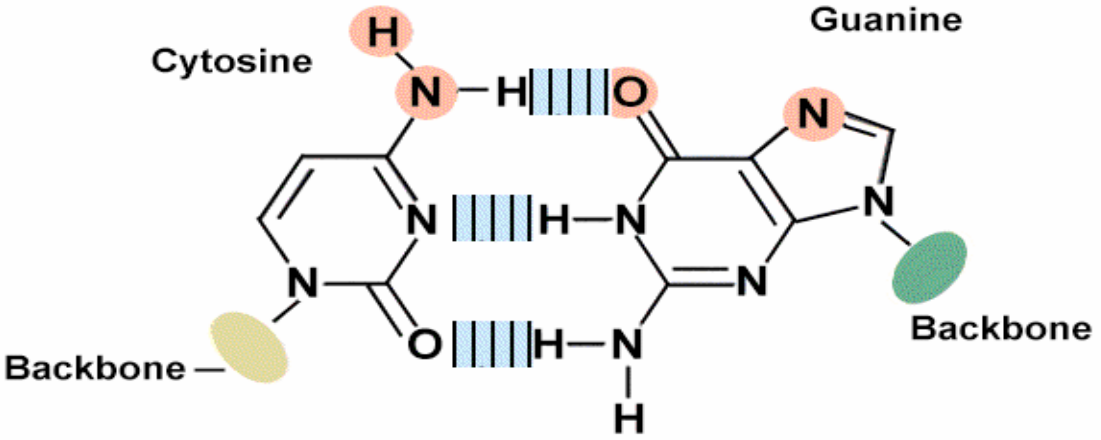

(a)
5′ end
3′ end
C
A
G
OH
Free 5' end
Free 3' end
P
S
A
C
G
T
5'
3'

Nucleic acids (structure cont.)

Secondary structure: base pairing

- Is the Watson–Crick model, DNA consists of two double helix.
- The two strands run in opposite directions
  - **The double helix** is held in place by
    - **Two** hydrogen bonds (A-T) and
    - **Three** hydrogen bonds (G-C)


Thymine
Adenine
CH
O
H
N
H
N
N
N
N
N
N
O
Backbone
Backbone
Hydrogen bonds


Cytosine
Guanine
H
N
H
O
N
N
H
N
N
N
N
O
H
N
H
Backbone
Backbone

Nucleic acids (structure cont.)

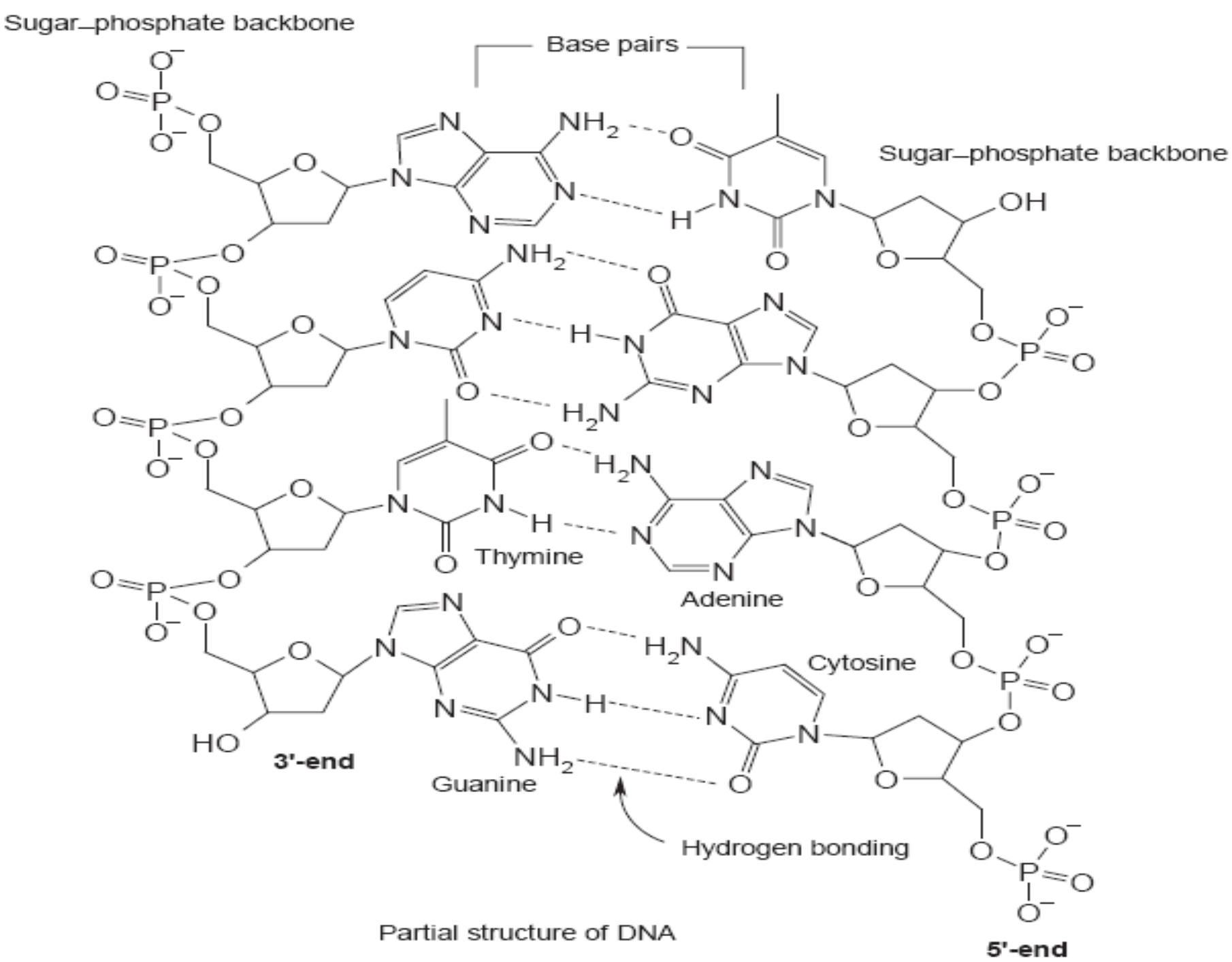
- The two strands of the double helix coil in such a way that two types of 'groove' are formed:
  - a major groove 1.2 nm wide and
  - a minor groove 600 pm wide.

Nucleic acids (structure cont.)

- Many proteins interact in the space of the major groove, where they make sequence-specific contacts with the bases.
- In addition, a few proteins are known to make contacts via the minor groove.

Nucleic acids (structure cont.)

- A number of flat, polycyclic molecules
  - fit sideways into the groove between the strands and
  - intercalate, or insert themselves, b/n the stacked base pairs
- Many cancer causing and cancer preventing agents
  - exert their actions through intercalating with DNA.



Partial structure of DNA

Nucleic acids (structure cont.)

- While the sugar–phosphate backbone of DNA is completely regular, the sequence of heterocyclic base pairs along the backbone can be of different permutations.
  - Sugar-Phosphate backbone is invariable
  - Base region of DNA variable
  - It is the precise sequence of base pairs that carries the genetic information.

Nucleic acids (cont.)

C. Chemistry of Nucleic Acids

- The role of DNA as a repository of genetic information depends in part on its **inherent stability**.
  - The chemical transformations that do occur are generally very slow in the absence of an enzyme catalyst.
  - The long-term storage of information without alteration is so important to a cell

Nucleic acids (Chemistry cont.)

- However, even very slow reactions that alter DNA structure can be physiologically significant.
- Other, nondestructive alterations also occur and are essential to function, such as the strand separation that must precede DNA replication or transcription.

Chemical modification of Nucleic Acid

- After a DNA molecule has been assembled,
  - it may be chemically modified
- The chemical modification can be
  - Deliberate - by special enzymes (Enzymatic)
  - Accidental - by oxidation, ionizing radiation, or the action of chemical carcinogens.
- DNA can also be cleaved and degraded by enzymes called nucleases.

Chemical modification cont.

- **Example of enzymatic Transformations of Nucleic Acids- Methylation**
  - Three types of natural methylation have been reported in DNA.
  - Cytosine can be modified
    - either on the ring to form 5-methylcytosine or
    - on the exocyclic amino group to form N4-methylcytosine.
  - Adenine may be modified to form N6-methyladenine.

Chemical modification cont.

- Special enzymes called DNA methyltransferases are responsible for this methylation;
  - they recognize specific sequences within the DNA molecule so that only a subset of the bases is modified.
- Natural methylation has many cellular functions.

Chemical modification cont.

Non-enzymatic Transformations of Nucleic Acids

- Purines and pyrimidines, along with the nucleotides of which they are a part, undergo a number of spontaneous alterations in their covalent structure.

Nonenzymatic transformations cont.

- The rate of these reactions is generally *very slow,* but they are physiologically significant because of the cell's very low tolerance for alterations in its genetic information.

Nonenzymatic transformations cont.

- Alterations in DNA structure that produce permanent changes in the genetic information encoded therein are called **mutations,**
  - Much evidence suggests an intimate link between the accumulation of mutations in an individual organism and the processes of aging and carcinogenesis.

Nonenzymatic transformations cont.

- Some of the important reactions of nucleic acids include:
  - **Methylation**
    - Methylations of the bases or of the deoxyribose are sometimes induced by carcinogens.
    - These usually lead to mispairing of the bases during replication and have to be removed if they are not to become mutagenic.

Nonenzymatic transformations cont.

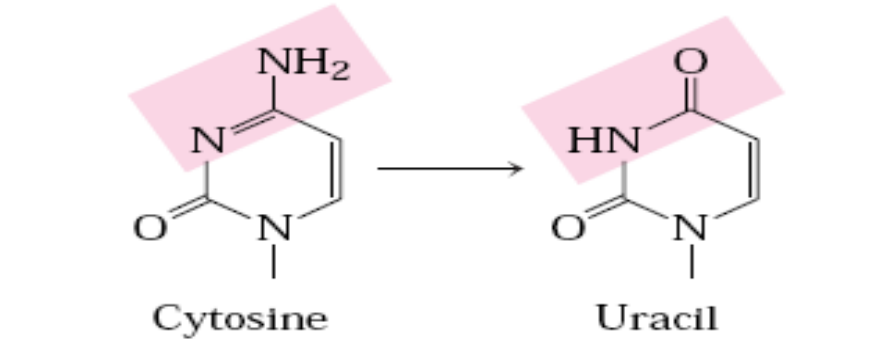
- **Oxidation**

  - Possibly the most important source of mutagenic alterations in DNA is oxidative damage.
  - Excited-oxygen species such as hydrogen peroxide, hydroxyl radicals, and superoxide radicals arise during irradiation or as a byproduct of aerobic metabolism.

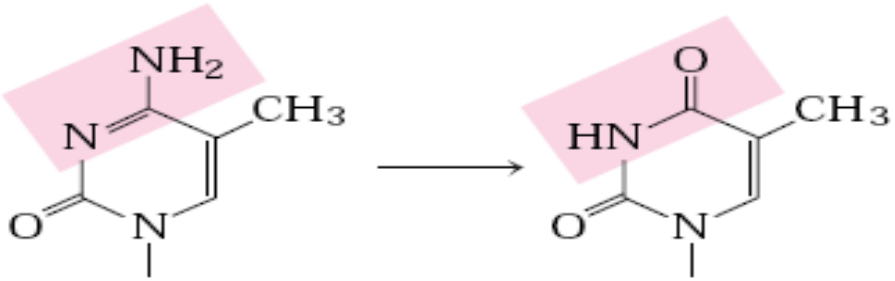
Oxidation cont.

- Of these species, the hydroxyl radicals are responsible for most oxidative DNA damage.
- Oxidative damage by free radicals or strong oxidizing agents can cause a variety of lesions that are mutagenic if not repaired.

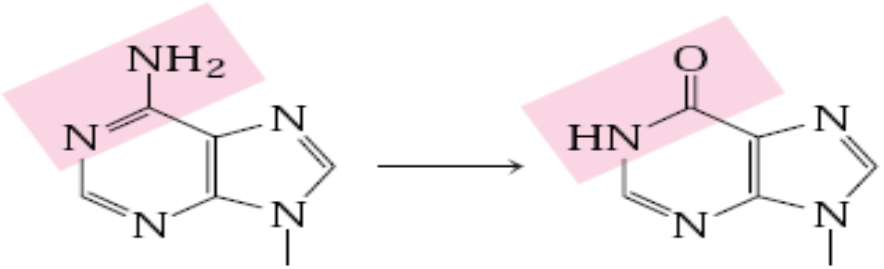
- **Deamination**
  - Several nucleotide bases undergo spontaneous loss of their exocyclic amino groups (**deamination**)



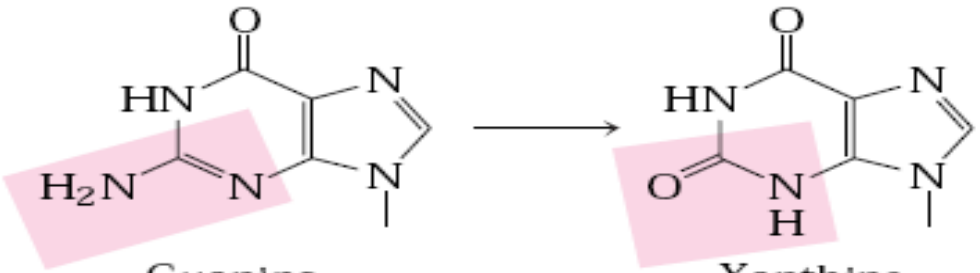
Cytosine → Uracil



5-Methylcytosine → Thymine



Adenine → Hypoxanthine



Guanine → Xanthine

Nonenzymatic transformations cont.

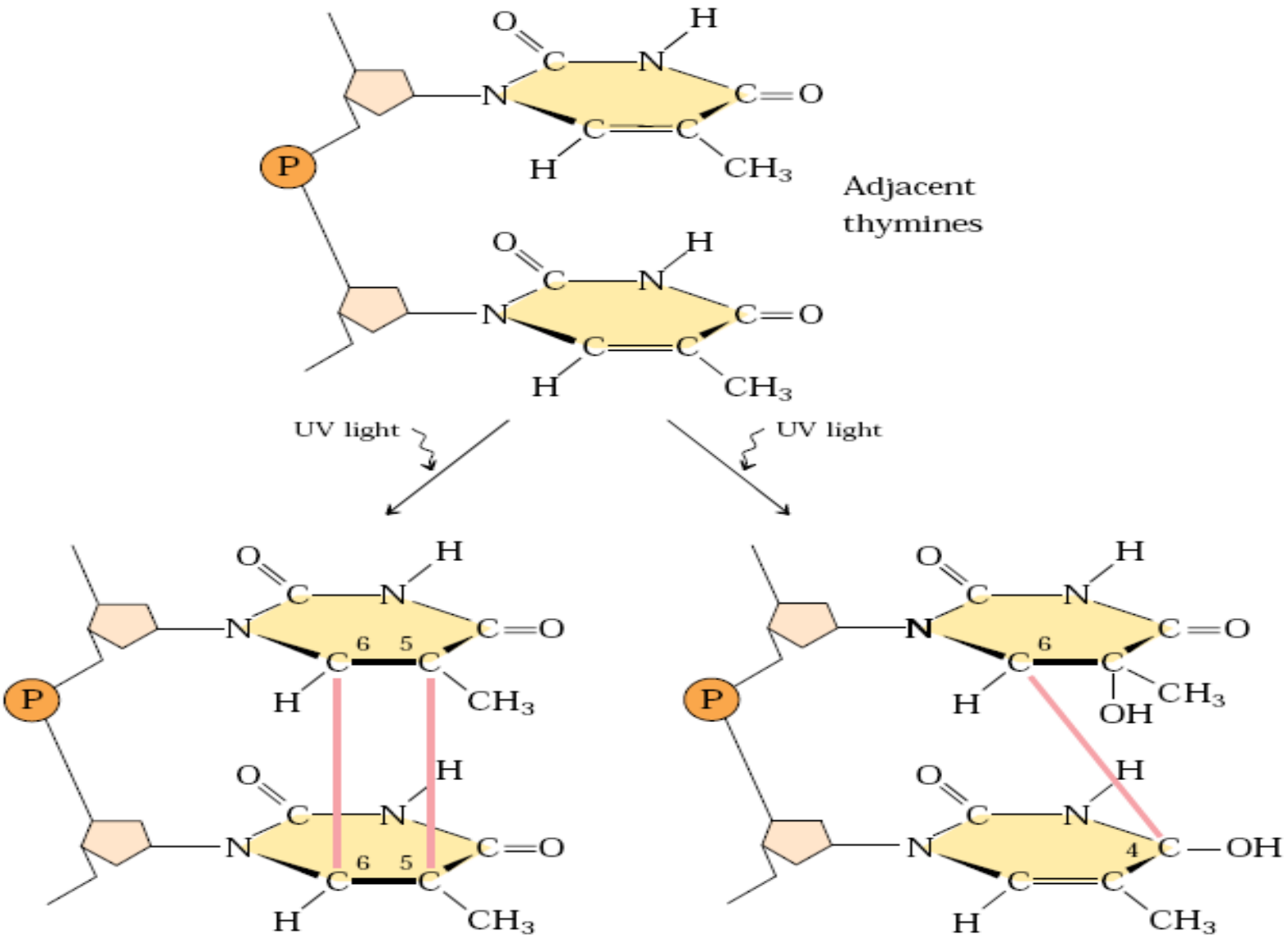
- **Hydrolysis**
  - Hydrolysis of the N-glycosyl bond between the base and the pentose is another important reaction of nucleic acids especially DNA.

Nonenzymatic transformations cont.

- **UV light induced condensation**
  - UV light induces the condensation of two ethylene groups to form a cyclobutane ring.
  - In the cell, the same reaction b/n adjacent **pyrimidine bases** in nucleic acids forms cyclobutane pyrimidine dimers.

Nonenzymatic transformations cont.

- This happens most frequently b/n adjacent **thymidine residues** on the same DNA strand.
- A second type of pyrimidine dimer, called a 6-4 photoproduct, is also formed during UV irradiation.


Adjacent thymines
UV light
UV light
Cyclobutane thymine dimer
6-4 Photoproduct

Nonenzymatic transformations cont.

- Ionizing radiation (X-rays and γ-rays) can
  - cause ring opening and fragmentation of bases as well as
  - breaks in the covalent backbone of nucleic acids.
- Virtually all forms of life are exposed to energy-rich radiation capable of causing chemical changes in DNA.

Nonenzymatic transformations cont.

- DNA also may be damaged by reactive chemicals introduced into the environment as products of industrial activity.
  - Such products may not be injurious per set but may be metabolized by cells into forms that are injurious.
- Two prominent classes of such agents are
  - deaminating agents and
  - alkylating agents

Nonenzymatic transformations cont.

- **Nitrous acid**, formed from organic precursors such as nitrosamines and from nitrite and nitrate salts, is a potent accelerator of the deamination of bases.
- Anions such as bisulfite can deaminate cytosine to form uracil

Nonenzymatic transformations cont.

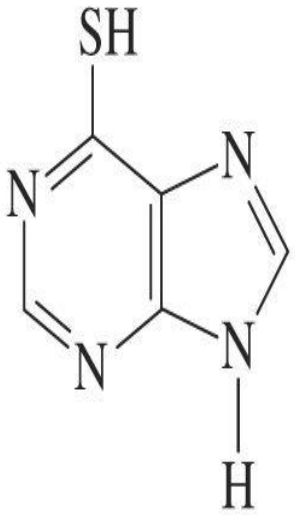
- Alkylating agents can alter certain bases of DNA.
  - For example, the highly reactive chemical dimethylsulfate can methylate a guanine to yield O-6-methylguanine, which cannot base-pair with cytosine.
  - Many similar reactions are brought about by alkylating agents normally present in cells, such as S-adenosylmethionine.

III. Significance of Purines and nuclic acids in pharmacy

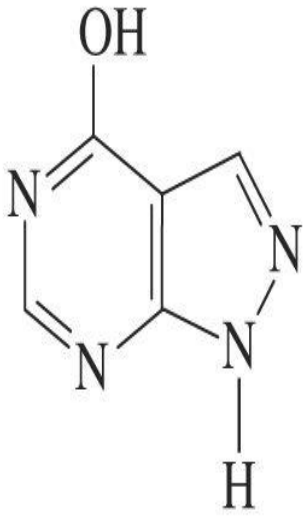
- The purine and pyrimidine bases
  - play an important role in the metabolic processes of cells through their involvement in the regulation of protein synthesis.
  - Thus, several synthetic analogues of these compounds are used to interrupt the cancer cell growth.
  - One such example is an adenine mimic, 6-mercaptopurine, which is a well known anticancer drug.

Significance of…cont.

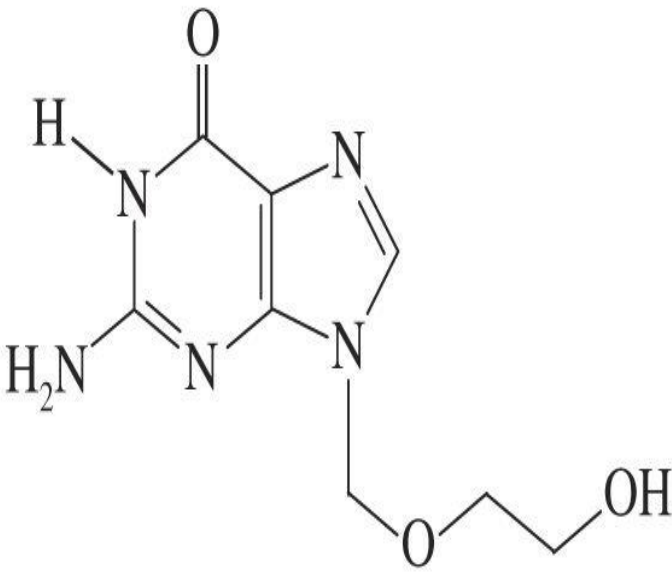
- **Examples of Purine skeleton related drugs**



6-Mercaptopurine



Allopurinol



Acyclovir

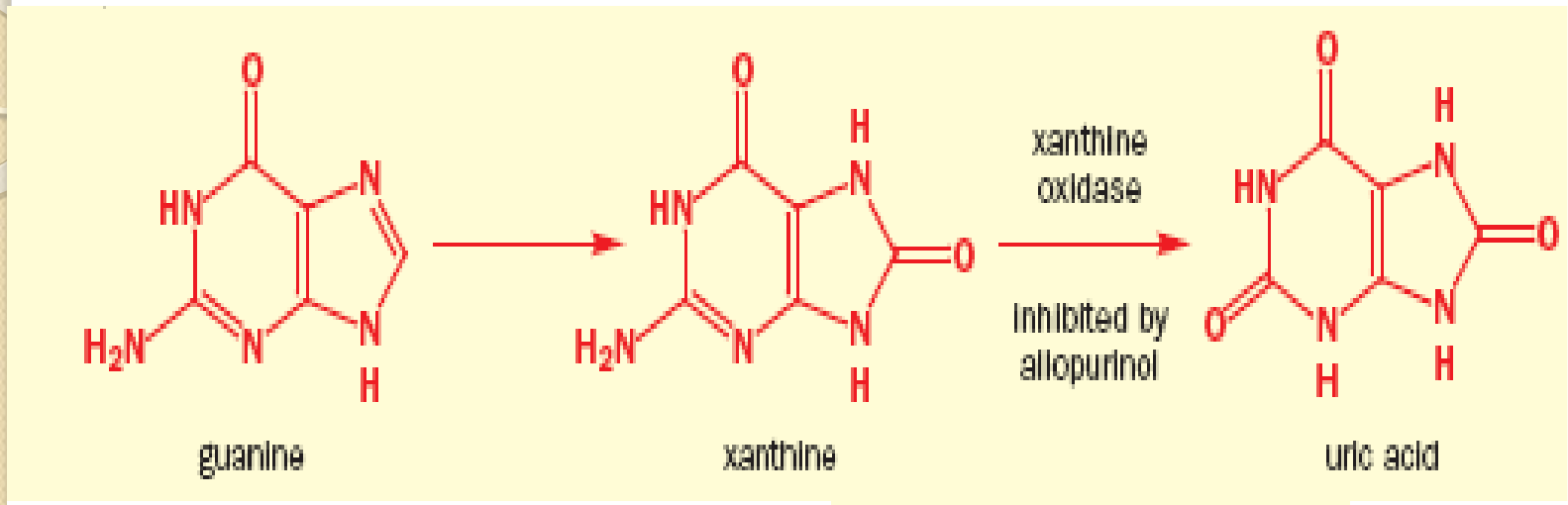
Significance of…cont.

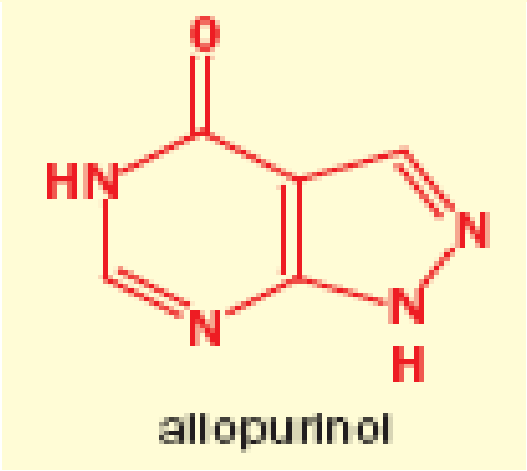
- **Medical applications:**
  - **6-mercaptopurine** is used for acute leukemia in children,
  - **Allopurinol** is used for treatment of gout and
  - **Acyclovir** is used against herpes viruses

Gout treatment

- **Allopurinol**
  - Is a drug used in the treatment of **gout**, a disease that is characterized by severe inflammation in one or more of the joints of the extremities
  - It closely resemble uric acid
    - Two of the carbonyl groups have gone and the imidazole ring has been replaced by a pyrazole ring

Gout treatment cont.





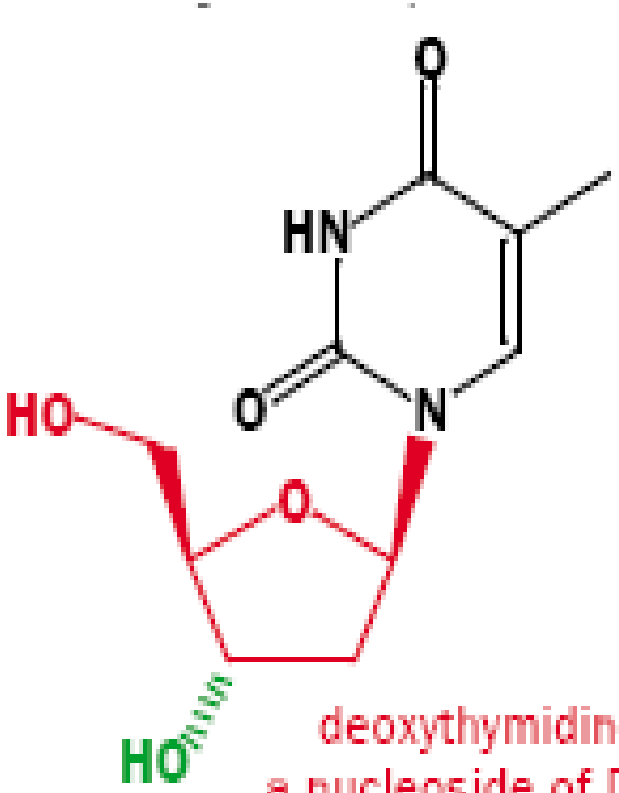
Gout treatment cont.

- **Purines** from DNA are degraded in the body to **xanthine**, which is oxidized to **uric acid**.
- Allopurinol binds to the enzyme xanthine oxidase but inactivates it by not reacting.
- In fact it imitates not uric acid but the true substrate xanthine in a competitive fashion.

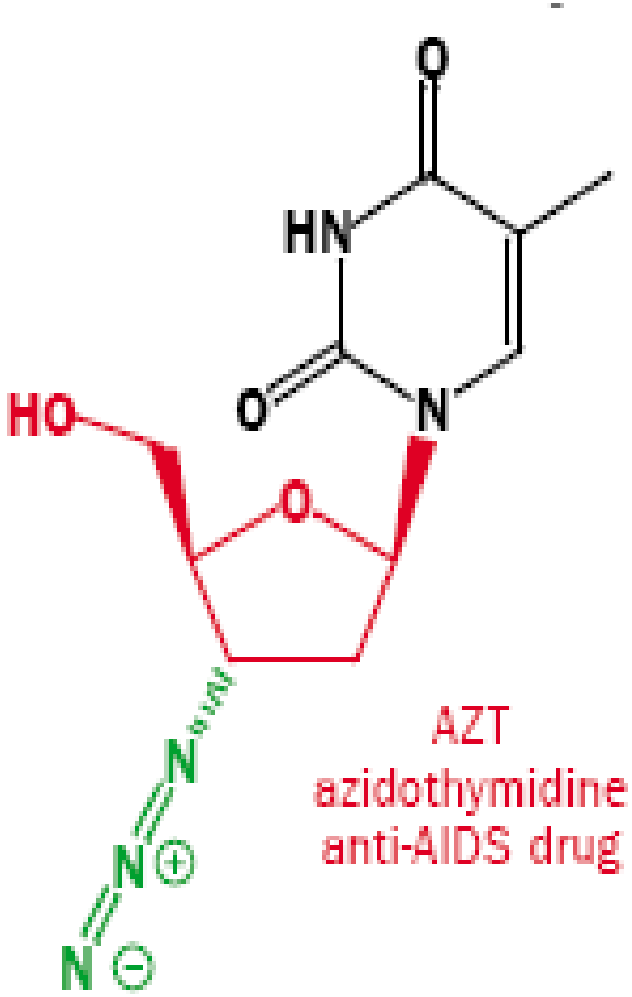
AIDS treatment

- **AIDS is being treated with modified nucleosides**
  - Modified nucleosides have proved to be among the best antiviral compounds.
  - The most famous anti-AIDS drug, **AZT (zidovudine)**,
    - Is a slightly modified DNA nucleoside (3'-azidothymidine)
    - It has an azide at C3' instead of the hydroxyl group in the natural nucleoside.

AIDS treatment cont.



deoxythymidine
a nucleoside of DNA



AZT
azidothymidine
anti-AIDS drug

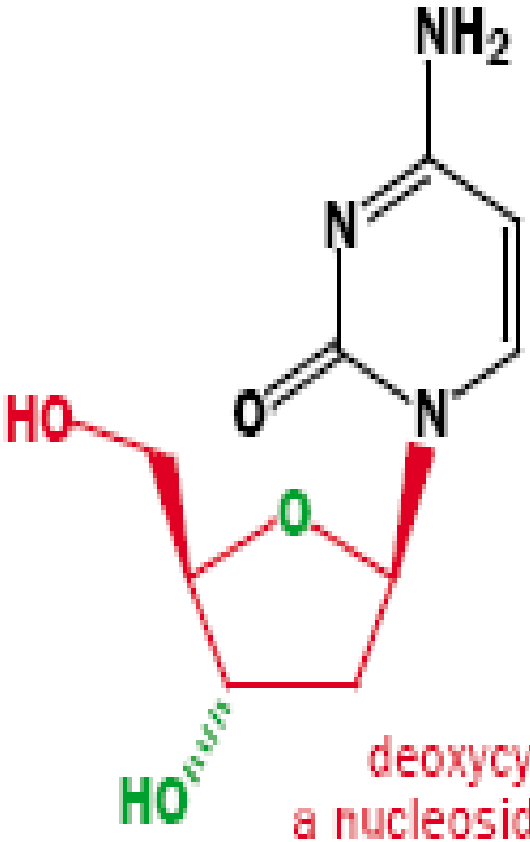
AIDS treatment cont.

- spectacular success against HIV and AIDS have been achieved by
  - using a combination of **AZT** and
  - a much more modified nucleoside **3-TC (lamivudine)** which is
    - active against AZT-resistant viruses.

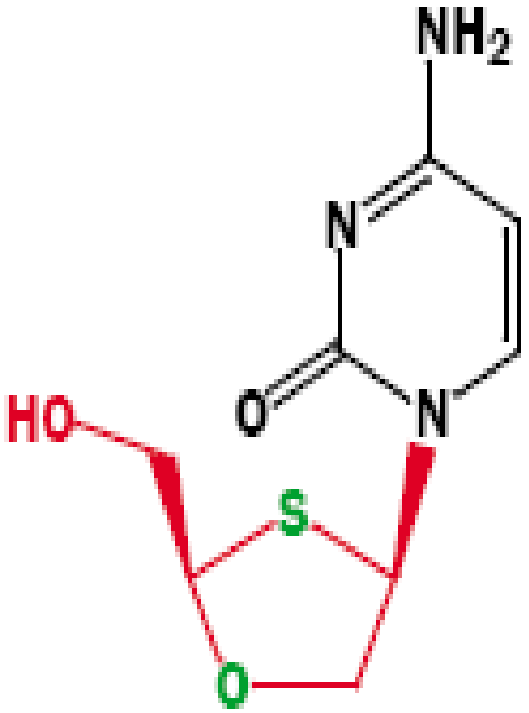
AIDS treatment cont.

- This drug is based on cytosine but
  - the sugar has been replaced by a different heterocycle
  - though it is recognizably similar especially in the stereochemistry.

AIDS treatment cont.



deoxycytidine
a nucleoside of DNA



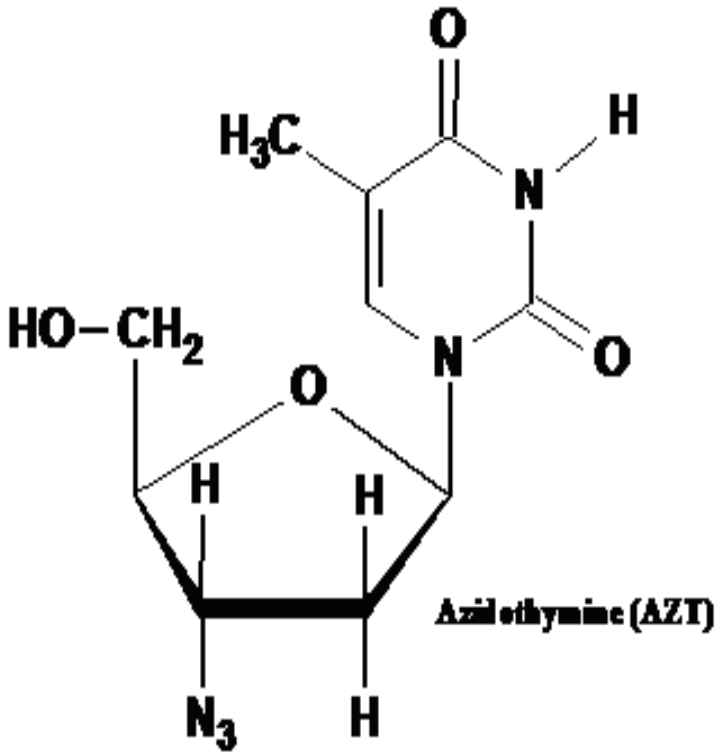
3-TC
lamivudine
anti-AIDS drug

AIDS treatment cont.

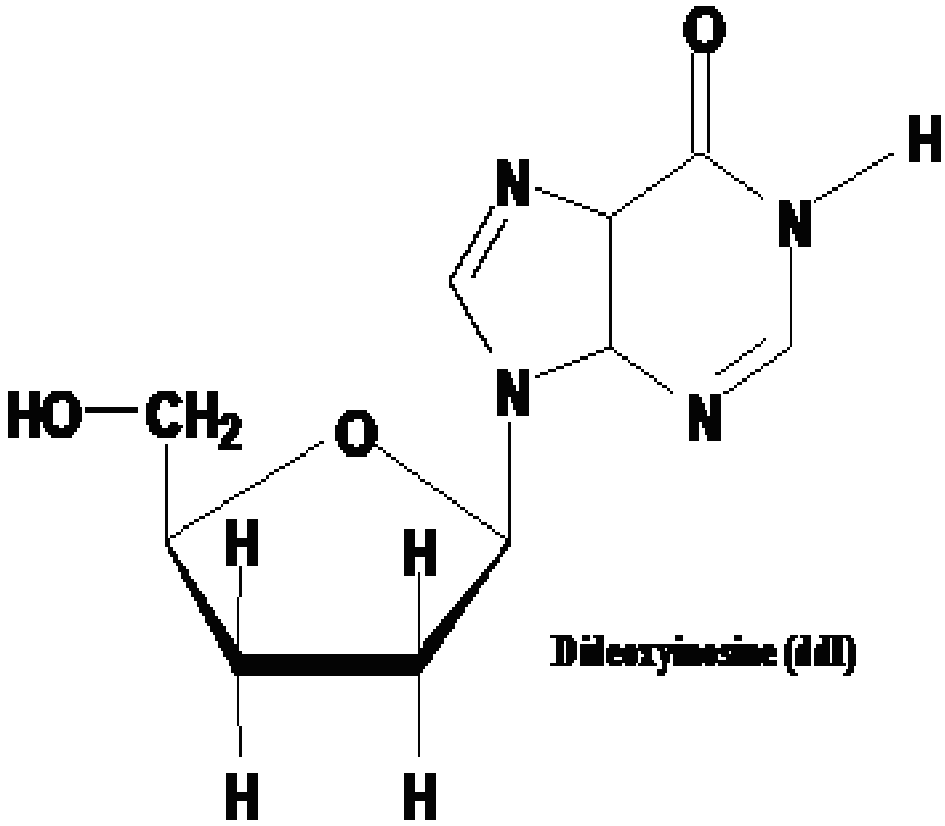
- Thus one type of AIDS treatment prevents reverse transcription of the viral DNA.
  - When altered nucleosides such as AZT and ddI are incorporated into viral DNA,

➢ the virus is unable to replicate.

AIDS treatment cont.



Azidothymine (AZT)



Dideoxyinosine (ddI)

AIDS treatment cont.

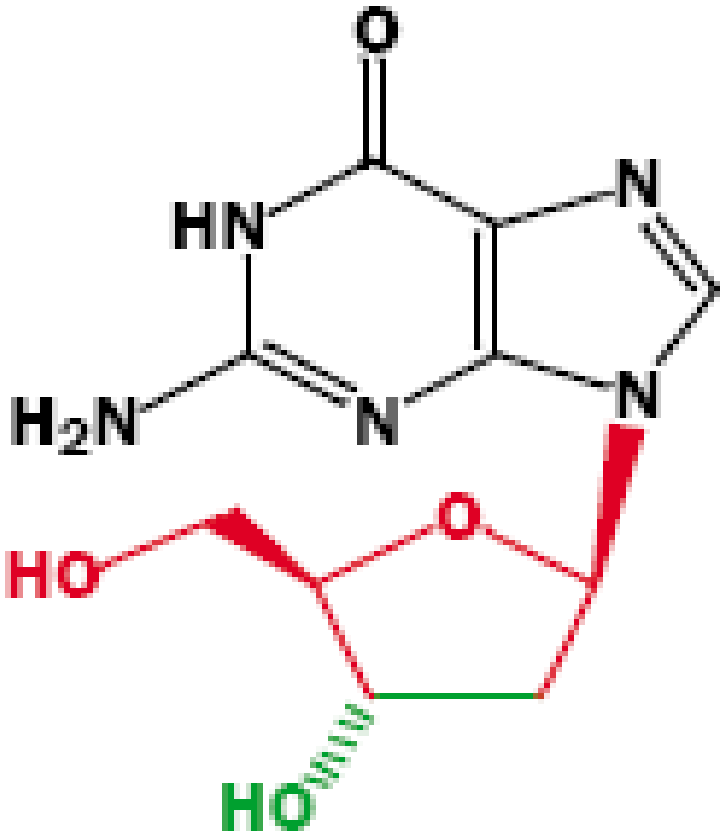
- Another type of AIDS treatment involves protease inhibitors such as saquinavir, indinavir, and ritonavir.
- Protease inhibitors modify the active site of the protease enzyme, which prevents the synthesis of viral proteins.

Herpes treatment

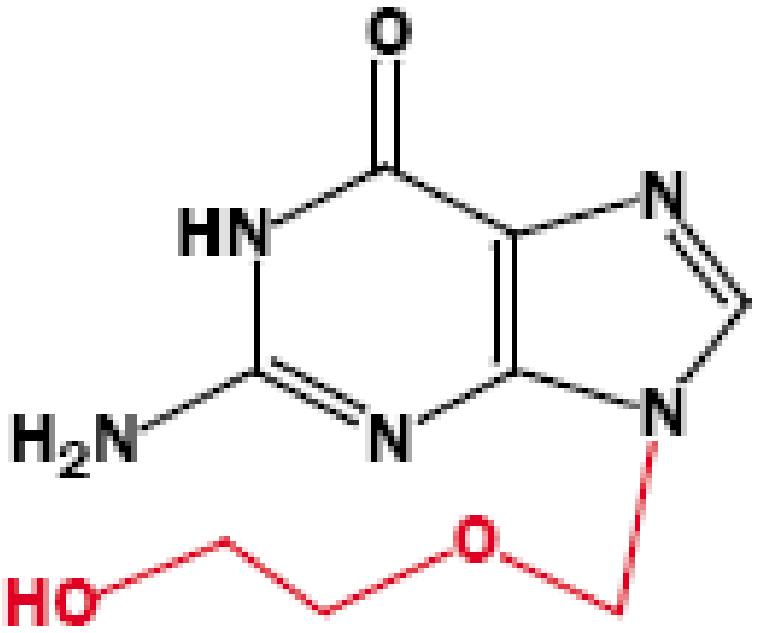
- **Acyclovir** (Zovirax)
  - is another antiviral drug used in cold sore (herpes) treatment.
  - It is a modified guanosine in w/c only a ghost of the sugar remains.
  - There is no ring at all and no stereochemistry.
  - The bottom edge of the sugar ring has been done away with so that a simple alkyl chain remains.

Herpes treatment cont.

deoxguanosine
a nucleoside of DNA



acyclovir
(Zovirax)
anti-herpes drug



Herpes treatment cont.

- This compound has proved amazingly successful as an antiviral agent and
  - it is highly likely that more modified nucleosides will appear in the future as important drugs.
- Many of ant-herpes agents are nucleoside analoges

End of topic